REMARKS

Claims 1, 2, 4-10, and 12-15 are pending in the present application.

The claims are not obvious

Claims 1, 2, 4-10 and 12-15 are rejected under 35 U.S.C. §103(a) for alleged obviousness over Dualan *et al.*, U18299 nucleotide sequence and abstract ("*Dualan*"), in view of Taylor *et al.*, 1999 *Drug Disc. Today*, *4*(12):562-567 ("*Taylor*"); Baracchini *et al.*, U.S. Patent No. 5,801,154 ("*Baracchini*"); Hayes *et al.*, Mol. Cell. Biol., 1998, 1:240-249 ("*Hayes*"); and Krishnaoorthy *et al.*, Biochem., 1997, 36:960-969 ("*Krishnaoorthy*"). Applicants respectfully request reconsideration of the rejection, as the combination of the cited art does not render the claims obvious. In support of Applicants' position, a Declaration Under 37 C.F.R. §1.132 of Dr. Susan Freier is attached.

As best understood, the Office Action appears to assert that the present invention is obvious in view of a combination of the cited art, on the basis that:

> 1) Dualan allegedly teaches "the same human DDB1 mRNA transcript that applicants claim as a target (Office Action, page 2);
>
> 2) Taylor allegedly provides an expectation of success in that by screening "only 3-6 sequences ... [the art skilled will] find one that inhibits 66-95% *in vitro*."(Office Action, page 2);
>
> 3) Baracchini allegedly teaches "methods of making and using antisense molecules to inhibit targets of known sequence" (Office Action, page 3); and
>
> 4) Hayes and Krishnaoorthy allegedly teach "motivation for inhibiting said target" (Office Action, page 3).

As discussed in greater detail below, the Office has failed to provide a *prima facie* case of obviousness. Accordingly, Applicants disagree with the Office's position.

The Cited References

Dualan reports a nucleotide sequence that comprises 4193 nucleotides that encodes human damage-specific DNA binding protein DDBa p127 subunit (DDB1). Dualan fails to teach or suggest any compound targeted to DDB1.

Taylor reports general high-throughput approaches to target validation and gene function determination. Taylor fails to teach or suggest DDB1, less still any compound targeted to DDB1.

Baracchini reports antisense oligonucleotide modulation of multidrug resistance-associated protein using a variety of chemically modified oligonucleotides. Baracchini fails to teach or suggest damage-specific DDB1, less still any compound targeted to DDB1.

Hayes reports that a putative DNA repair protein (DDB) can function as a transcription partner of transcription factor E2F1. Hayes fails to teach or suggest any compound targeted to DDB1.

Krishnamoorthy reports antibody inhibition of DDB as a means for testing the function of DDB. Krishnamoorthy fails to teach or suggest any compound targeted to DDB1.

The Office asserted that although:

> Applicants have amended the claims to read on antisense targeted to human DDB1, and further claims that such antisense must be able to inhibit said DDB1 by at least 60% ... [t]hese claim limitations are not sufficient to clear the claims from the instant rejection, because Taylor et al. teach that only 3-6 sequences need to be screened in order to find one that inhibits 66-95% *in vitro*. Taylor et al. thus teaches that one of ordinary skill in the are, using art recognized methods, would have an expectation of success in finding compounds that inhibit at least 60%.

(Final Rejection, page 2). Applicants do not agree with the Examiner's assertions.

MPEP §2143 sets forth three criteria that must be met to establish a *prima facie* case of obviousness.

> ***First***, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. ***Second***, there must be a reasonable expectation of success. Finally, the

> prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP §2143 (emphasis supplied). The Examiner must first establish motivation to combine or modify the references before the expectation of success can even be considered. The Examiner cannot rely upon a reasonable expectation of success to establish motivation. Such reliance is clearly improper.

As set forth above, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from appellants' disclosure, see for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would ***impel*** one skilled in the art ***to do what the patent applicant has done***. (citations omitted; emphasis added)

Significantly, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention.

The Office has failed to provide proper motivation to combine the cited references. The cited references fail to discuss a compound 8 to 50 nucleobases in length

targeted to a 5'-untranslated region, a start codon region, a coding region, a stop codon region, or a 3'-untranslated region of a nucleic acid molecule encoding human Damage-specific DNA binding protein 1, p127, (SEQ ID NO:3), wherein the compound inhibits the expression of human Damage-specific DNA binding protein 1, p127 by at least 60%. The cited references fail to cite one another. Further Taylor and Baracchini fail to even discuss DDB1. Baracchini provides an extensive list of potential modifications and synthetic schemes for oligonucleotides but the Examiner has provided no reasoning why a skilled artisan would pick certain of the modifications listed by Baracchini and then combine them with teachings of other references. Taylor further does not provide sufficient teachings that would have led one skilled in the art to do anything other than "try" ***unspecified*** methodology in predicting active antisense oligonucleotides. The "art-established methods" of Taylor cited by the Examiner are ***devoid*** of any information that would allow the art-skilled to practice that which Taylor discusses. Indeed, in proper context, the Taylor reference reports:

> The best target sites are still determined empirically, although improvements in the potency of ONs and in the algorithms used for predicting accessible sites on the target mRNA have drastically reduced the number of oligonucleotides that must be screened to find one that is effective. Previous recommendations required the screening of 30-60 ONs per gene. Using high affinity chimeric oligomers and a bioinformatics program to select accessible sites, Woolf and coworkers have found that screening 3-6 oligomers per target is sufficient to find one that inhibits the gene with 66-95% efficiency (Sequitur, Natick, MA, USA) (unpublished data), significantly reducing the time and labor required to identify active ONs.

It appears that the only potential sources of motivation to combine the references are either provided by Applicants' disclosure itself (which would be an impermissible use of hindsight reconstruction), or merely because the subject matter of the claimed invention is a promising field for experimentation, although the prior art provides only general guidance as to particular form of the claimed invention or how to achieve it. See, *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). The "obvious to try" standard is clearly inappropriate and exists when a general disclosure "may pique the scientist's

curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *Id.*

The Office has failed to identify a motivating force that "would impel one skilled in the art to do what the patent applicant has done." Indeed, there are many avenues to take when desiring to modulate the activity of a protein involved in a disease pathway. For example, one skilled in the art may choose to investigate the role of peptides/proteins, antibodies, or even small molecules that modulate DDB1. None of the cited references provide any motivation to choose any particular avenue to modulate DDB1 activity, let alone specifically choose oligomeric compounds.

What the Office appears to suggest is that the claimed invention would have been obvious because it would have been possible to modify DDB1 with oligonucleotide compounds. The mere possibility that the prior art can be modified, however, does not itself provide the requisite motivation to do so. *In re Dien*, 152 U.S.P.Q. 550 (C.C.P.A. 1967) (incentive to seek improvement of existing process held to not render change made by applicant obvious, even where the change was one capable of being made from theoretical point of view). The mere possibility for modification and improvement is not the "motivating force" that the Patent Office Board of Appeals and the Federal Circuit have invariably required. If it were, then no modification would ever lack motivation since some change is always possible. Quite to the contrary, an invention is obvious under the patent laws only when the claimed means for effecting an improvement -- as opposed to the possibility of trying any and all means -- is suggested by the prior art. *In re Shaffer*, 108 U.S.P.Q. 326 (C.C.P.A. 1956) (references, viewed by themselves and not in retrospect, must suggest doing what applicant has done). Significantly, neither of the cited references would have motivated persons of ordinary skill to make the substantial modifications that would have been necessary to produce the claimed invention. It is only with the improper use of hindsight and with the benefit of the Applicants' disclosure that one can discern the desirability of the particular invention now claimed.

Again, the alleged motivation, at most, raises an inappropriate "obvious to try" standard. Indeed, the court made it clear that it is improper to reject claims as "obvious to

try" where the motivation to combine references arises merely because the subject matter of the claimed invention is a promising field for experimentation, although the prior art provides only general guidance as to particular form of the claimed invention or how to achieve it. *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Without more specific suggestions in the prior art, there is insufficient motivation to combine the cited references. Furthermore, "focusing on the obviousness of substitutions and differences, instead of the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Son*, 16 U.S.P.Q.2d 1923, 1927 (Fed. Cir. 1990).

The Office also stated that "it is noted that applicants have apparently not disputed that the instant rejection met the proper criteria in showing that the elements are taught and that motivation exists in determining that the claimed invention is obvious, That is, applicants have not argued that motivation is lacking, or that the instant combination of references fails to teach all the elements of the claimed invention." Applicants do not agree for at least two reasons.

As discussed above, Applicants assert that motivation to combine references is lacking and that no reasonable expectation of success has been provided. At most, the Office appears to suggest that it is "obvious to try" the combination of the references. Upon a close reading of the cited references it is clear that no motivation to combine the references exists. Such lack of motivation to combine the cited references is confirmed by Dr. Susan Freier in the attached "Declaration under 37 C.F.R. §1.132, who states in paragraph 5 that one of skill in the art would not be motivated to combine references as suggested by the Office.

In addition to establishing an impelling motivation, in order to set forth a legally sufficient *prima facie* case of obviousness, the Patent Office must also show that the cited references teach or suggest a claimed invention with a ***reasonable expectation of success***. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531-32 (Fed. Cir. 1988). The Office asserts that one of ordinary skill in the art would have a reasonable expectation of success in finding antisense compounds that successfully inhibit the expression of DDB1 using routine and well established methods, referring to the Taylor reference (see, pages 4-5 of the Office Action). The Taylor reference, however, does not establish a reasonable

expectation of success in obtaining oligonucleotide compounds that would inhibit DDB1 by at least 60%. Although the Examiner cites Taylor in an attempt to supply a reasonable expectation of success, Taylor fails to provide any expectation of success, much less a reasonable expectation of success. Taylor discusses general high-throughput approaches to target validation and gene function determination. At best, Taylor sets forth ***unsupported*** assertions about the ease of identifying target sites on any gene for oligonucleotides that bind the target and inhibit gene expression.

It is well known to the art skilled that the determination of target sites on a gene that permits one to identify suitable, highly inhibitory oligonucleotides for that gene is not a simple or easy process. One of skill in the art would not expect to be able to identify an oligonucleotide that inhibits expression with 66-95% efficiency by screening only 3-6 oligonucleotides for a particular gene.

Taylor also fails to teach how to select the 3-6 oligonucleotides to be screened in order to find an oligonucleotide that inhibits expression with 66-95% efficiency. Indeed, Taylor neither discloses the identity of the program for screening oligonucleotides nor the manufacturer of such a program so as to enable one skilled in the art to practice the teachings discussed therein. For example, one skilled in the art examining the Taylor reference would not be able to determine: 1) what it is about the chimeric oligonucleotides makes them chimeric (i.e., undisclosed chemical modifications), 2) what bioinformatics program should be used (i.e., undisclosed bioinformatics program, parameters, etc.), or 3) information for initial selection of accessible sites, based upon the disclosure in Taylor. Instead, Taylor, rather than actually teaching one skilled in the art details sufficient to carry out such methods, simply refers to "unpublished data." Thus, Taylor acts only as general guide (in the sense that it reports that active oligonucleotides can generally be found) for screening oligonucleotides and fails to provide any details sufficient for one skilled in the art to carry out any particular methodology. See, *Chester v. Miller*, 906 F.2d 1574, 15 U.S.P.Q.2d 1333 (Fed. Cir. 1990) (reference must put subject matter at issue into possession of the public through an enabling disclosure). One skilled in the art having examined the entirety of Taylor would, at most, conclude that it may be "obvious to try" to design compounds targeted to particular regions of a gene. Without more specific suggestions in the prior art, there is insufficient "expectation of

success." Accordingly, Taylor is a non-enabling reference and thus may not be used as prior art.

Applicants also submit that one of skill in the art would not look to Taylor for either motivation to combine references or to establish a reasonable expectation of success. As discussed above, Taylor does not even discuss the Damage-specific DNA binding protein 1, p127 gene. Because each gene is different, one skilled in the art would not reasonably expect success in achieving at least 60% inhibition in the expression of a different gene with a different set of oligonucleotides that are specific to the different gene or mRNA. The level of inhibition of expression that is observed for one target has no bearing on the level of inhibition of expression expected for a different target. (See Declaration, paragraph 9).

The Office appears to conclude that simply because screening assays for evaluating the inhibitory activity of oligomeric compounds are available, one skilled in the art would, thus, have a reasonable expectation of success in obtaining oligomeric compounds that would inhibit the expression of DDB1 by at least 60%. That screening assays are available would, at most, provide a reasonable expectation of success of being able to screen oligomeric compounds for inhibitory activity. The mere fact that screening assays are available and routine, however, has no bearing on whether one skilled in the art would have a reasonable expectation of success in obtaining oligomeric compounds that inhibit the expression of a particular gene by a particular amount.

Applicants submit herewith a Declaration of Dr. Susan Freier, one of skill in the art of oligonucleotide technology. In paragraph 6, Dr. Freier declares that it is not possible to currently predict the level of inhibition of expression achieved with any particular oligomeric compound prior to carrying out the appropriate experiments. In paragraph 6, Dr. Freier declares that it is not reasonable to expect for any particular gene or mRNA that oligomeric compounds having at least 66% inhibition in the expression will be obtained. Thus, simply because screening assays are available and may be routine, one skilled in the art would not have a reasonable expectation of success in obtaining oligomeric compounds that will inhibit the expression of DDB1 by at least 60%. Therefore, even if one skilled in the art were motivated to combine the cited references in the manner indicated in the Office Action (and Applicants maintain that no such

motivation has been established), one skilled in the art would not have had a reasonable expectation of success.

Applicants respectfully remind the Office that when an applicant submits evidence traversing a rejection, the examiner ***must*** reconsider the patentability of the claimed invention based on consideration of the ***entire record*** with due consideration to the persuasiveness of any arguments. *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). Applicants respectfully request that the Office reconsider the pending rejection under 35 U.S.C. § 103 in view of the attached declaration.

Applicants remind the Examiner that *In re Alton*, 76 F.3d 1168, 1174 (Fed. Cir. 1996) holds that it is not sufficient for the Examiner to simply say that a Declaration is insufficient, stating that "the summary dismissal of the declaration, without an adequate explanation of why the declaration failed to rebut the Board's prima facie case . . ." was error. Accordingly, if the Examiner deems the attached Declaration insufficient to overcome the pending rejection, Applicants request a detailed explanation of why the Declaration fails to rebut the obviousness rejection.

In view of the foregoing, Applicant respectfully submits that the Office has failed to establish a *prima facie* case of obviousness. In particular, the Office has failed to provide any motivation that would ***impel*** one skilled in the art to modify the cited references so as to produce Applicants' claimed inventions with a reasonable expectation of success. Accordingly, Applicants respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

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Conclusion

In view of the foregoing, Applicant submits that the claims as amended are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Respectfully submitted,

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